幼少期の腸内環境と社会行動

菊水　健史
麻布大学獣医学部・麻布大学ヒトと動物の共生科学センター

略歴

1970年　鹿児島県生まれ
1995年　東京大学農学部獣医学科卒業　獣医師免許取得（D.V.M.）
1995－1997年　三共株式会社・神経科学研究所 研究員
1997－2007年　東京大学大学院農学生命科学研究科（動物行動学研究室）助手
2007－2009年　麻布大学獣医学部 コンパニオンアニマル研究室 准教授
2007年－現在　同大学 教授

研究分野

社会神経内分泌学、ヒトと動物の絆、感情、オキシトシンシグナル、動物行動学

主な科学的業績

・**イヌの「よろこびの涙」**：オキシトシンによって媒介される、飼い主との再会時にイヌが感情的な涙を流す現象を世界で初めて実証。
・**オキシトシンによるアイコンタクトの増強**：点鼻によるオキシトシン投与がイヌの飼い主への視線を増加させ、それによって飼い主側のオキシトシン分泌も高まることを明らかにし、ヒトとイヌという異種間での絆形成の神経機構を示した。
・**飼い主のオキシトシン上昇効果**：イヌと飼い主の相互注視によりヒトの尿中オキシトシン濃度が上昇し、絆形成に寄与することを発見。
・**社会行動と腸内細菌叢**：げっ歯類モデルを用いて、社会的ストレスや環境因子が腸内細菌叢を変化させ、その構成と感情行動との関連性を明らかにした。

要旨

脳 - 腸軸（brain-gut axis）は、脳と腸の相互的な情報伝達系として、現在では動物における基本的な生理機能の一つとして広く認識されている。近年の研究では、腸内細菌叢の構成が、腸粘膜や腸管神経系との局所的な相互作用にとどまらず、中枢神経系（CNS）とも影響を及ぼし合っていることが示唆されている。たとえばマウスの研究では、腸内細菌叢の変化が記憶や学習、不安行動といった脳内の神経化学や行動に影響を及ぼすことが示された[1)]。腸内マイクロバイオームは、神経、内分泌、免疫、代謝の経路を通じて中枢神経系と直接的に相互作用する可能性がある[2-5)]。腸内細菌は迷走神経を活性化させ、脳内の炎症性サイトカインを刺激することも示されている[6)]。神経内分泌学的には、腸内細菌叢はストレス応答を司る視床下部 - 下垂体 - 副腎軸（HPA 軸）を調節し、認知機能や気分障害にも関与する[2, 4)]。

我々は、無菌マウス（GF マウス）が SPF マウスと比べてオープンフィールドテストにおいてアリーナ中央にいる時間が短く、個体間距離が長いことを見出し、不安行動が上昇していることを見出した。また、GF マウスでは前頭前皮質の BDNF（脳由来神経栄養因子）が減少し、ストレスと関連するといわれる ΔFosB の mRNA が増加していた。GF と SPF マウスでは腸内細菌叢の構成に当然差があったが、離乳後に同居させると細菌叢の構成が類似し、行動や BDNF・ΔFosB mRNA 発現の群間差も消失した。これらの結果は、発達期において細菌叢が社会性や不安に関連する神経系に影響を及ぼし、同種個体との相互作用を通じて腸内環境に応じた社会行動が形成されうることを示唆している[7)]。

さらに我々は、母性行動がマウスにおいて母系的に伝達されるか、また腸内細菌が関与しているかを検討した。早期離乳（EW）した雌マウスは、通常離乳（NW）マウスよりも、自分の子への舐め・毛づくろい（LG）行動が少ないことが確認された。この母性行動の特徴は、全てのメスマウスが通常離乳されたにもかかわらず、2世代目でも認められた。その後の里誤操作実験では、LG の頻度は生物学的母親ではなく養育母によって影響を受けることが示された。最後に、EW または NW マウスの糞便由来の腸内細菌を無菌マウスに移植し、その後育児行動を評価したところ、EW 由来の腸内細菌を移植されたマウスでは LG 行動が有意に低下した。これらの結果は、母性行動のうち LG が世代を超えて伝達され、腸内細菌の垂直伝播がこのプロセスに関与していることを示している[8)]。

イヌ（Canis familiaris）は、人類が最初に家畜化した動物であり、現在では数百の犬種が存在している。家畜化の過程で､イヌは気質･行動･認知能力に基づく強い選択を受け、独自の認知能力を獲得した[9)]。これらの人間に似た能力は、人と犬との間の絆形成、すなわち異種間の絆にも関与していると考えられる。我々は、イヌがヒトとの絆を形成するためにオキシトシンを介したポジティブ・ループを形成するのに対し、オオカミはこのループを示さないことを明らかにし、家畜化の過程でイヌが生物学的な絆形成メカニズムを獲得したことを示した[10)]。また近年では、イヌの飼育が人間の健康に良い影響を与えるという疫学的報告も増えている。私たちの研究でも、イヌを飼っている思春期の子どもは、社会性が高く、問題行動が少ない傾向が認められた[11)]。さらに、腸内細菌叢が中枢神経系に影響を与えることをふまえて、子どもたちの口腔から採取した細菌叢を無菌マウスに移植したところ、イヌの飼い主由来の細菌叢を持つマウスでは社会性が向上することが確認された。このことから、イヌの飼育による向社会性の向上の一部は、腸内細菌叢の変化による可能性が示された。ヒトとイヌは、相互に影響を与えながら、互いに利益をもたらす関係を築いてきたと考えられる（未発表データ）。

これらの結果は、発達段階にある動物が周囲の環境、とりわけ他個体との相互作用を通じて多様な腸内細菌を獲得することが適応的意義を持ち、それによって適切な社会行動が形成される可能性を示唆している。

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Brain-Gut interactions and development of social behavior

Takefumi Kikusui
Laboratory of Human-Animal Interaction and Reciprocity, School of Veterinary Medicine, Azabu University.
Human and Animal Symbiosis Science, Azabu University
Research and Advancement Support Division

Brief Curriculum Vitae

1970: Born in Kagoshima Pref. Japan.
1995: Graduated from Veterinary Medicine University of Tokyo. D.V.M.
1995-1997: Research associate at the Sankyo Neuroscience Research Institute.
1997-2007: Assistant professor at the Graduate School of Agricultural and Life Sciences (Veterinary Ethology Lab) at the University of Tokyo.
2007-2009: Associate professor at the Companion Animal Research Laboratory, Azabu University Veterinary Medicine.
2007-present: Professor.

Research Interests

Social neuroendocrinology, human-animal bonding, emotion, oxytocin signaling, animal behavior.

Key Scientific Achievements

- Dog tears of positive emotion: First demonstration that dogs secrete tears during positive reunions with their owners, mediated by oxytocin release.
- Oxytocin-enhanced gazing: Showed that administering intranasal oxytocin to dogs increases their eye gaze toward owners, boosting owner oxytocin levels—supporting interspecies bonding mechanisms.
- Owner oxytocin elevation: Observed that mutual gaze from dogs increases urinary oxytocin in humans, reinforcing attachment bonds.
- Social behavior and microbiome: In rodent models, revealed that how social stress and environmental factors alter the gut microbiome in animal models, revealing links between microbial composition and emotional behavior.

Abstract

The brain-gut axis, a reciprocal communication between two organs, is now widely recognized as one of the fundamental physiological functions in animals. Recent research has suggested that the composition of the gut microbiome does not only interact locally with intestinal cells and the enteric nervous system but also with the central nervous system (CNS). For example, in mice studies, changes in

gut microbiota influence brain chemistry and behavior, such as memory, learning, and anxiety related behavior[1]. The microbiome in the intestine has the potential to interact with the CNS directly via neural, endocrine, immune, and metabolic pathways[2-5]. It has been shown that gut microbes activate the vagus nerve, which is one of the main information carriers from the gut to the brain and stimulate inflammatory cytokines in the brain[6]. Neuroendocrinologically, the gut microbiota can modulate the hypothalamic-pituitary-adrenal axis that controls the stress response and plays a role in cognition and mood disorders[2, 4].

We fond that GF mice spent less time in the center area of the arena and there were longer inter-individual distances compared with SPF mice. GF mice also had decreased brain-derived neurotrophic factor (BDNF) and increased ΔFosB mRNA in the prefrontal cortex compared to SPF mice. There were differences in the gut microbiome composition between GF and SPF mice; however, if cohabitating after weaning, then their microbiome composition became equivalent and group differences in behavior and BDNF and ΔFosB mRNA expression disappeared. These results demonstrate that the bacterial community can modulate neural systems that are involved in sociability and anxiety during the developmental period and suggest that sociability and anxiety can be shaped depending on the microbiome environment through interaction with conspecifics[7].

Moreover, we aimed to determine whether the matrilineal transmission of maternal behavior occurs in mice and whether the microbiota is involved. We first observed that early weaned (EW) female mice showed lower levels of maternal behavior, particularly licking/grooming (LG) of their own pups, than normally weaned (NW) female mice. This difference in maternal behavioral traits was also observed in the second generation, even though all mice were weaned normally. In the subsequent cross-fostering experiment, the levels of LG were influenced by the nurturing mother but not the biological mother. Finally, we transplanted the fecal microbiota from EW or NW mice into germ-free (GF) mice raising pups. The maternal behaviors that the pups exhibited toward their own offspring after growth were analyzed, and the levels of LG in GF mice colonized with microbiota from EW mice were lower than those in GF mice colonized with microbiota from NW mice. These results clearly indicate that, among maternal behavioral traits, LG is intergenerationally transmitted in mice and suggest that the vertical transmission of microbiota is involved in this process. This study demonstrates the universality of the intergenerational transmission of maternal behavioral traits and provides new insights into the role of microbiota[8].

The dog (*Canis familiaris*) was the first animal to be domesticated, with hundreds of different dog breeds recognized today. During the domestication process, dogs were subjected to a strong selection process according to their temperament, behavior, and cognitive abilities[9], and acquired their unique cognitive abilities during domestication.

These human-like unique abilities might also be related with interspecies' bonding, namely human-dog bonding. We revealed that dog showed oxytocin mediated positive-loop for forming bonds with humans, and wolves did not show this positive loop with humans, suggesting that dog have acquired biological bond mechanisms in the process of domestication[10]. Nowadays, there are many epidemiologic reports on the benefits to humans of owning dogs that have lived with humans for so long. We also found that dog ownership improved the well-being of adolescents. These children were also more sociable and had fewer behavioral problems[11]. At the same time, we examined the gastrointestinal microbiome known to affect the central nervous system and found that the effects of dog ownership differed between dog-owner and non-dog-owner children. When the bacterial flora collected from the children was administered to sterile mice, the mice became more prosocial. Thus, it was found that some of the benefits of dog-ownership may be due to changes in the bacterial flora. It is feasible that dogs and humans have established a mutually beneficial relationship while influencing each other (unpublished data).

These results imply the adaptive significance of developing animals acquiring a various gut microbiota in their environment, especially in their interactions with other individuals, and accordingly developing appropriate social behaviors.

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